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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT		ATTY. DOCKET NO.
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EXAMINER

18M1/0903

MARY J. WILSON
NIXON & VANDERHYE P.C.
1100 NORTH GLEBE ROAD 8TH FLOOR
ARLINGTON VA 22201-4714

GAMBEL, P

ART UNIT	PAPER NUMBER
1806	14

DATE MAILED: 09/03/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 6/10/97

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 33, 37, 42-48 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 33, 37, 42-48 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

DETAILED ACTION

1.Since this application is eligible for the transitional procedure of 37 CFR 1.129(a), and the fee set forth in 37 CFR 1.17(r) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.129(a). Applicant's first submission after final filed on 6/10/97 (Paper No. 13) has been entered.

2. Applicant's amendment, filed 6/10/97, is acknowledged.
Claims 33, 37, 41, have been amended
Claims 45-48 have been added.
Claims 34-36, 38-40 have been canceled.

Claims 1-5 and 8-32 are canceled have been canceled previously

Claims 33, 37 and 42-48 are pending.

3. The text of those sections of Title 35 USC not included in this Action can be found in a prior Office Action.

4. Claims 33, 37 and 42-48 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of copending application Serial No. 08/289,532. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications are drawn essentially to the same use of CD4- and/or CD8-specific antibodies in the generation of immunological tolerance.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant requested that this be held in abeyance upon the indication of allowable subject matter.

5. Upon reconsideration of the instant disclosure and of the instant claims, drawn to treating human autoimmunity with non-depleting antibodies, the following 112,first paragraph, is set forth.

The specification is objected to and claims 33, 37 and 42-48 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. In evaluating the facts of the instant case, the following is noted:

Applicant has not disclosed how to use non-depleting CD4 and/or CD8 monoclonal antibodies with or without depleting CD4 and/or CD8 monoclonal antibodies as therapeutic agents to induce tolerance to the claimed broad range of antigens in humans. There is insufficient information or nexus with respect to the scope of the claimed methods to use applicant's invention for the following reasons.

It is noted that the previous 112, first paragraph, rejection had been withdrawn in view of applicant's amended claims and arguments in conjunction.

However, upon a review of the instant specification as filed, the following is noted.

Page 8, paragraph 1 of the instant specification discloses that the depleting and non-depleting CD4 and CD8 monoclonal antibodies can be raised in any convenient manner. However, there is no direction or guidance as to the use or necessity of humanized antibodies in achieving therapeutic effects in treating human autoimmunity.

Panayi et al., Choy et al., Levy et al., Connoly et al. (Arthritis and Rheumatism, 1996) all disclose the positive therapeutic effects of either humanized or primatized non-depleting CD4 antibodies in treating human rheumatoid arthritis.

However, the instant specification does not provide guidance for such recombinant forms of antibodies to treat human autoimmunity. Concerning antibody therapy in humans, Harris et al. states that there is widespread acceptance that there is little future for the use of rodent monoclonal antibodies for in vivo human therapy (page 42, column 2) and that repeated dosing with chimeric antibodies is ineffective due to residual anti-idiotypic responses (page 42, column 3) (Tibtech, 1993; 892 of record). Applicant has not provided guidance to circumvent such problems. Furthermore, achieving long-term unresponsiveness with non-depleting antibodies in humans would require multiple dosing; therefore, such therapies would require humanized antibodies even more so. The Crowe declaration under 37 C.F.R. § 1.132, filed 9/26/96, concerning HAMA responses is acknowledged. However, Crowe appears to rely on the use of chimeric or humanized antibodies to alleviate the limitations of antibody therapy in humans. Again, the instant specifiction does not provide such guidance to use such humanized antibodies in treating human autoimmunity and it is the use of humanized antibodies that is critical to the success of non-depleting antibodies in alleviating some symptoms of arthritis. In contrast, the specification appears to rely upon convenient monoclonal antibody production and not humanized antibodies to achieve the desired therapeutic effect encompassed by the claims.

Page 6, paragraph 1, of the instant specification as filed discloses treating autoimmune diseases such as multiple sclerosis or rheumatoid arthritis. However, the objective evidence for treating human autoimmunity with non-depleting (humanized) antibodies is directed only to rheumatoid arthritis. There is insufficient objective evidence to support the treatment of other autoimmune diseases commensurate in scope with the claimed invention. The Crowe declaration under 37 C.F.R. § 1.132, filed 9/26/96, is acknowledged. Crowe et al. refers to a number of autoimmune diseases that have been treated with CD4-specific antibodies, however it appears that such successes relied upon chimeric or humanized CD4-specific antibodies and not simply non-depleting monoclonal CD4-specific antibodies, as disclosed by the specification as filed. Further, the instant disclosure does not disclose these other autoimmune diseases, but rather directs the artisan only to rheumatoid arthritis and multiple sclerosis. Schmidt et al. (Nervenarzt, 1996; see English Abstract and translation provided) disclose that there is no indication for the treatment of multiple sclerosis with monoclonal anti-T cell antibodies at the present time. Therefore, the specification as filed does not the differences between autoimmune therapeutic interventions and directs the artisan to one (of only two disclosed) that is not appropriate.

There is insufficient objective evidence to support that non-depleting CD4-/CD8-specific antibodies can achieve long-term immunological unresponsiveness to autoantigens in humans. As indicated above, there is evidence that humanized non-depleting antibodies can alleviate certain symptoms of rheumatoid arthritis. However, the claimed invention is drawn to long-term immunological unresponsiveness, not just alleviation of symptoms. Also, the claimed invention is drawn to achieving such long-term immunological unresponsiveness to any autoantigen, thereby effective for any autoimmune disease.

Although the applicant in conjunction with the Crowe declaration, has exemplified and relied upon some success with the instant methods for achieving unresponsiveness for certain antigens in certain mouse strain combinations with non-immunogenic rat antibodies, there is insufficient objective evidence or nexus that such therapy would work for any autoantigen in humans, encompassed by the claims and the intent of the invention. Applicant has not enabled that long-term unresponsiveness with non-depleting CD4-/CD8-specific antibodies, including non-humanized antibodies, can be achieved in human autoimmunity. Evidence of particular murine examples of tolerance induction across weak or defined antigenic barriers in experimental models or evidence of alleviation of rheumatoid arthritis with humanized non-depleting CD4-specific antibodies would not be predictive for the successful induction of long term immunological unresponsiveness to the scope of autoantigens in humans.

As pointed out in Paper No. 5, the efficacy of CD4-specific antibodies in immunosuppression have had varying success as an immunosuppressive reagents and that even long term transplant recipients require long term maintenance immunosuppression. The art has clearly recognized that each therapeutic target, including each autoimmune disease, cannot be considered as a whole and treatment selection must be considered with each targeted therapeutic intervention. Each targeted autoimmune disease would likely be different. Also, long term maintenance would require humanized antibodies, which is not disclosed in the specification as filed. As acknowledged in the art and by applicant's publications, it is clear that the antibody requirement for the induction of long-term unresponsiveness varies according to the immunological challenge. Also, the art-known resistance of autoimmunity to therapeutic intervention would be even more unpredictable when long-term unresponsiveness as claimed rather than alleviation of symptoms.

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective induction of immunological unresponsiveness with antibody therapy in humans, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods and products are effective for establishing long-term immunological unresponsiveness, commensurate in scope with the claimed invention.

6. Upon reconsideration of the art and in view of the claimed methods to induce long-term unresponsiveness in human autoimmunity, the previous art rejection under 35 U.S.C. § 103 has been withdrawn.

7. No claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee can be reached on (703) 308-2731. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1800 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014 or (703) 308-4242.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**lila.feisee@uspto.gov**].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Phillip Gambel, Ph.D.
Patent Examiner
Group 1800
September 2, 1997

PAULA K. HUTZELL
SUPERVISORY PATENT EXAMINER
GROUP 1800